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Proton Nuclear Magnetic Resonance Spectra of Sulfur Mustard and 2-Chloroethyl ethyl Sulfide in Selected Solvents

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14. ABSTRACT Our laboratory has a continuing interest in the analysis of sulfur mustard (HD) for the purpose of developing medical countermeasures. Nuclear magnetic resonance (NMR) spectroscopy is an important analytical technique for studying HD chemistry in simple solutions and in complex matrices. To support research in this area, we have developed a list of proton assignments for HD in a variety of suitable solvents. Because the half mustard 2-chloroethyl ethyl sulfide (CEES) is a non-surety analogue of HD we have added a list of proton assignments for CEES as well. In this study we used a 600 MHz NMR instrument to investigate 2-mM solutions of HD and CEES in deuterated solvents. These results can assist researchers in identifying HD and CEES in variety of solvents.					
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Introduction

Sulfur mustard (HD) is a vesicating chemical warfare agent that has been investigated by our laboratory for the express purpose of developing medical countermeasures. Solutions of HD are prepared in a variety of solvents to aid researchers. In these investigations nuclear magnetic resonance (NMR) spectroscopy has been playing a larger roll in the analysis and study of HD.^{1,2,3} In a recent work we measured the half-life of HD in D₂O.⁴ This study required a demonstration of proton NMR spectral assignments for HD in D₂O because previous studies^{5,6} indicated that solution of HD in aqueous media was followed instantaneously by hydrolysis. We verified the presence of HD by preparing 2-mM solutions of HD in D₂O containing 0.17 M NaCl. Five minutes after preparation of the solution, HD was extracted with deuterated hexane, and we demonstrated that the HD extracted had the same proton NMR spectra as a direct preparation of HD in deuterated hexane. The changes in the chemical shifts of HD in D₂O versus HD in deuterated hexane prompted us to undertake this study of HD and 2-chloroethyl ethyl sulfide (CEES) in a variety of available deuterated solvents.

We prepared 2-mM solutions of HD in nine solvents and 2-mM solutions of CEES in eight solvents. The proton spectra for each of these solutions demonstrate the changes that occur when HD and CEES respectively are placed in different solvents.

Materials and Methods

The sulfur mustard (2,2'-dichlorodiethyl sulfide, HD) employed in this study was obtained from the US Army Edgewood Chemical Biological Center (Aberdeen Proving Ground, MD). The purity was 97.5% as determined by NMR spectroscopy. 2-chloroethyl ethyl sulfide (CEES, 98%), deuterated solvents (99+ %), and 3-(trimethylsilyl)-1-propanesulfonic acid-d₄ were obtained from Sigma-Aldrich and used as received.

¹H NMR analysis

A previously prepared and frozen sample of 2 mM HD in D₂O was thawed to room temperature and thoroughly mixed by vortexing for three minutes. For the other solvents used in this work, 2-mM preparations were prepared volumetrically and stored at -70 °C. A 500 µL aliquot of the solution was transferred into 5-mm o.d. NMR tubes. All data were collected on a Varian Unity Inova 600 MHz NMR spectrometer using the standard ¹H pulse sequence. The WET pulse sequence for solvent suppression was utilized for the D₂O sample.⁷ Probe temperature was calibrated to 22.0 ± 0.1 °C by standard means. Samples were referenced to residual proto-solvent peaks. The D₂O sample was referenced to 3-(trimethylsilyl)-1-propanesulfonic acid-d₄ at 0 ppm.

Results

Tables 1 and 2 list chemical shift and coupling constants for HD and CEES in the various solvents studied. Figure 1 shows the number scheme used for the protons in the tables.

Figure 1. Structures of HD and CEES and numbering scheme for the protons of HD and CEES.

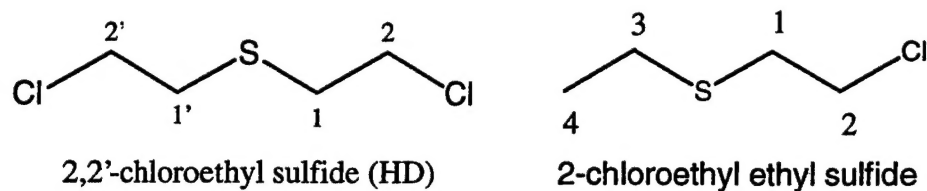


Table 1. Chemical shift (ppm) and coupling constants (Hz) for HD in various solvents

Solvent	H ^{2,2'}	H ^{1,1'}
CDCl ₃	3.65 (7.6)	2.92 (7.6)
CD ₃ CN	3.71 (7.6)	2.92 (7.6)
CD ₃ C(O)CD ₃	3.75 (7.6)	2.98 (7.6)
CD ₂ Cl ₂	3.66 (7.6)	2.92 (7.6)
CD ₃ S(O)CD ₃	3.76 (7.6)	2.92 (7.6)
C ₂ D ₅ OD	3.66 (7.6)	2.92 (7.6)
C ₃ D ₇ OD	3.70 (7.6)	2.96 (7.6)
C ₆ D ₁₄	3.60 (8.2)	2.92 (7.6)
D ₂ O ⁽⁴⁾	3.74 (7.6)	3.00 (7.6)

Table 2. Chemical shift (ppm) and coupling constants (Hz) for CEES in various solvents.

Solvent	H ²	H ¹	H ³	H ⁴
CDCl ₃	3.64 (7.6)	2.87 (7.6)	2.61 (7.6)	1.28 (7.6)
CD ₃ CN	3.69 (7.6)	2.87 (7.6)	2.60 (7.6)	1.23 (7.6)
CD ₃ C(O)CD ₃	3.70 (7.6)	2.87 (7.6)	2.62 (7.6)	1.23 (7.6)
CD ₂ Cl ₂	3.64 (7.6)	2.86 (7.6)	2.59 (7.6)	1.26 (7.6)
CD ₃ S(O)CD ₃	3.73 (7.6)	2.84 (7.6)	2.58 (7.6)	1.16 (7.6)
C ₂ D ₅ OD	3.62 (7.6)	2.83 (7.6)	2.59 (7.6)	1.24 (7.6)
C ₃ D ₇ OD	3.65 (7.6)	2.87 (7.6)	2.64 (7.6)	1.30 (7.6)
C ₆ D ₁₄	3.59 (8.2)	2.87 (7.6)	2.63 (7.6)	a

a. Peak obscured by methyl groups in solvent.

Discussion

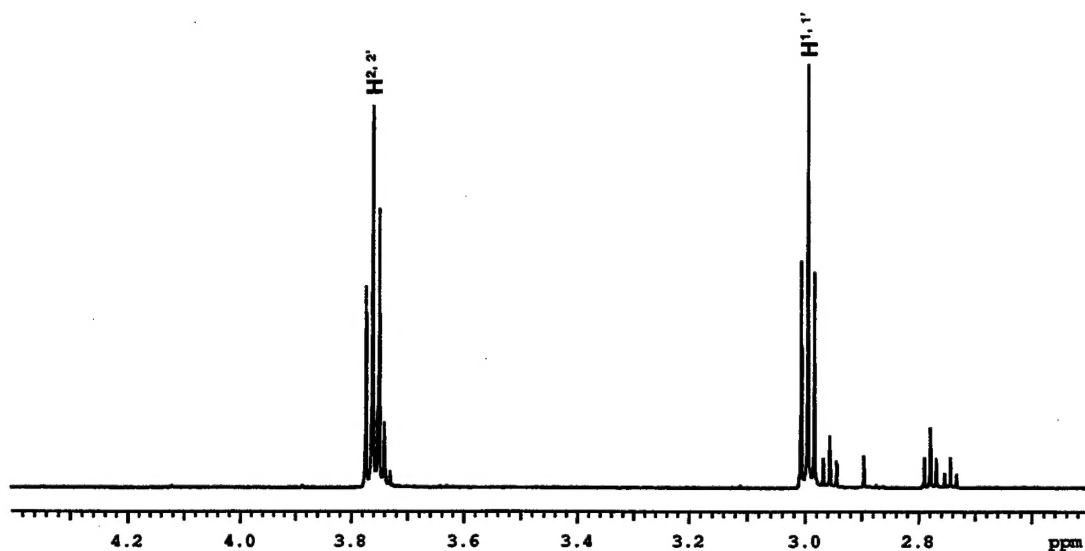
The influence of solvent on chemical shift for HD is relatively small (Table 1). For methylene protons H^{1,1'}, beta to the chloride, the greatest downfield change occurs in D₂O at 3.00 ppm. This can be attributed, at least in part, to the large dielectric constant of D₂O. HD has limited solubility⁸ in and reacts with D₂O to form deuterated thiodiglycol (TDG).^{4,8} In Figure 2, assignments for HD in D₂O are as follows: a region of overlapping methylene peaks for -CH₂-Cl in HD and -CH₂-OH in (TDG) at 3.7-3.8 ppm, methylene peaks for -S-CH₂ in HD at 3.00 ppm; peaks related to the reaction intermediate chlorohydrin at 2.96 and 2.78 ppm; 1,4 dithiane impurity at 2.90 ppm; and methylene peaks for -S-CH₂ in TDG at 2.74 ppm.

HD is much more stable in the remaining solvents in Table 1 than in D₂O. Figure 3 demonstrates this stability of HD in hexane. This stability gives the researcher a range of solvent choices to study HD. For methylene protons H^{2,2'}, alpha to the chloride, in HD there is a slightly larger influence of solvent on chemical shift.

The chemical shifts for CEES in Table 2 show little solvent influence. H¹ and H² chemical shifts for the one-armed mustard CEES are located near H^{1,1'} and H^{2,2'} values

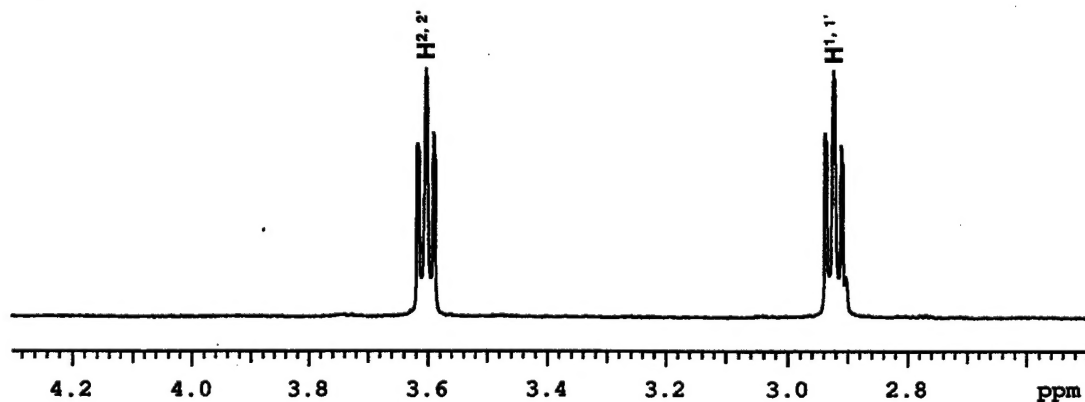
for HD, and this is expected based on the similar molecular environment for these methylene protons in CEES and HD (Figure 1). The remaining methylene protons H³ and methyl protons H⁴ are at 2.6 ppm and 1.2-1.3 ppm respectively. Representative proton NMR spectra are shown for CEES in deuterated chloroform, Figures 4, and deuterated acetonitrile, Figure 5. The additional peaks in these figures are due to water and non-deuterated solvent impurities. These data provide a reference source for the proton NMR chemical shifts of CEES and HD in the solvents studied.

Figure 2. HD in D₂O, containing 0.17 M NaCl, approximately 15 min. after preparation



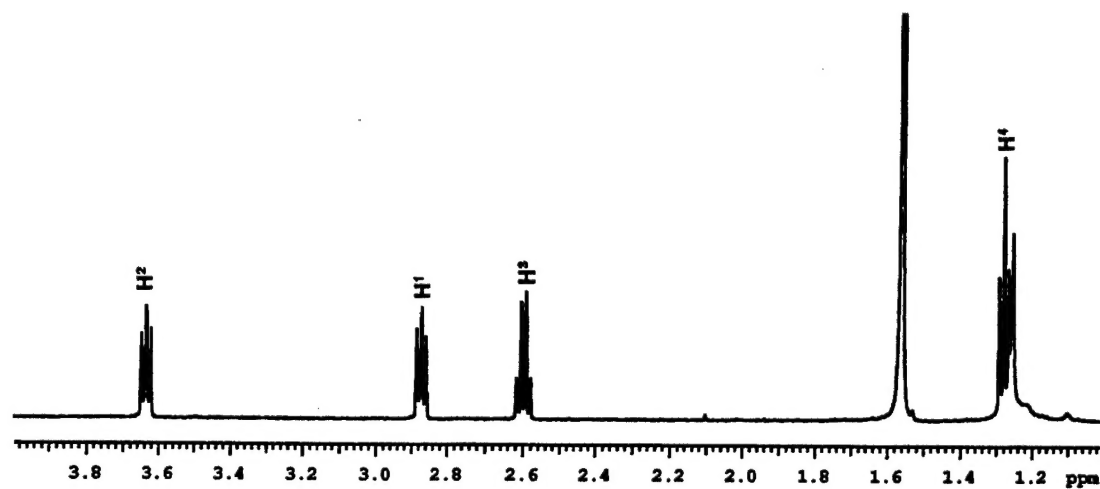
Proton NMR of HD and solvolysis products of HD in D₂O, containing 0.17 M NaCl, approximately 15 min after thawing and vortexing a 2 mM preparation.

Figure 3. HD in deuterated hexane



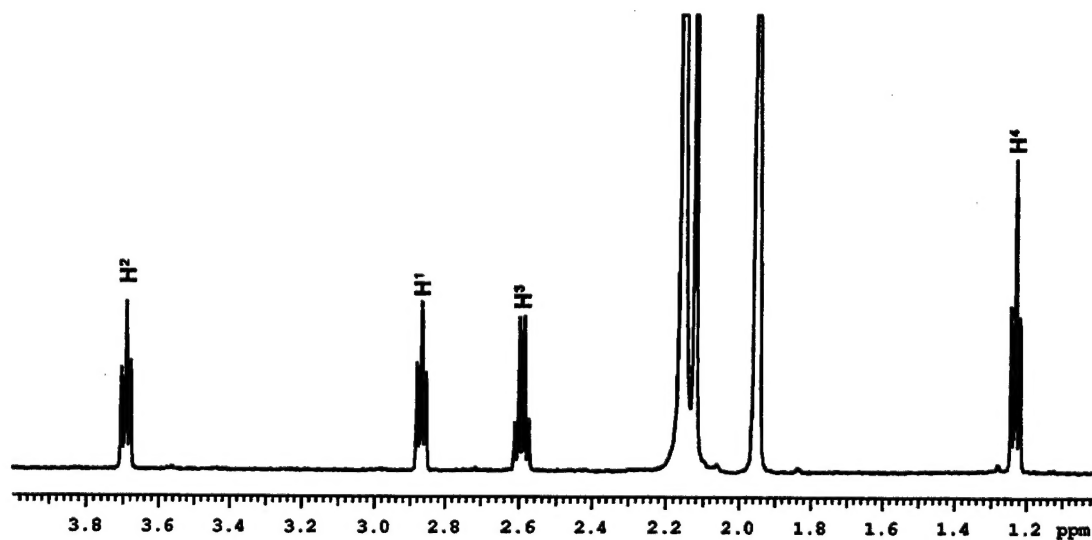
HD in deuterated hexane after extraction from HD in D₂O containing 0.17 M NaCl.

Figure 4. CEES in deuterated chloroform



CEES in deuterated chloroform at 2 mM; peaks in addition to those listed in Table 2 are due to water and non-deuterated solvent impurities.

Figure 5. CEES in deuterated acetonitrile



CEES in deuterated acetonitrile at 2mM; peaks in addition to those listed in Table 2 are due to water and non-deuterated solvent impurities.

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